Translated from French by the Ralph McEroy Co., Custom Division
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UNIT GALENICAL FORM FOR LOCAL HOMONOTHERAPY OF VAGINAL DRYNESS

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Inventor, and Inventor/Applicant (Only for United States only): MEIGNANT, Catherine [FR/FR]; 42-52, rue de l'Aqueduc, F-75010 Paris (FR).

Agent: DUPUIS-LATOUR, Dominque; Cabinet Bardehle, Pagenberg & Partner, 45, Avenue Montaigne, F-75008 Paris (FR).

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This galenical form in intended to a local treatment, essentially non systemic, of the vaginal dryness, particularly in menopaused women. It comprises a free natural oestrogen, particularly in micronized or vectorized, selected amongst 17β-estradiol and its salts in solution or in suspension in a lipophilic agent, with an oestrogen contents corresponding to a unit dose equivalent to 15 µg at the most, preferably less than 10 µg of 17β-estradiol, a bioadhesive gelifying hydrophilic agent, a gelifying agent of the lipophilic agent and a hydrodispersible agent. It comprises on the one hand, in the form of a soft capsule, an external solid hard or soft envelope containing gelatine and glycerin and, on the other hand, a liquid or semi-liquid internal phase containing the lipophilic agent with the oestrogen in solution or in suspension, the bioadhesion agent and the gelifying hydrophilic agent of the lipophilic agent. In a sustained release ovule form, it comprises a solid hard or semi-soft non aqueous homogeneous phase containing the lipophilic agent with the oestrogen in solution or in suspension, the hydrophilic bioadhesive gelifying agent, the gelifying agent of the lipophilic agent and the hydrodispersible agent.

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This invention concerns a proprietary drug for the local, essentially nonsystemic, treatment of vaginal dryness.

The disadvantages of vaginal dryness are well known, particularly in the menopausal woman: dyspareunia, urogenital atrophy that can cause urinary disorders, and risk of infection because of insufficiently developed flora.

One of the goals of the invention is to propose a proprietary drug which is appropriate for an essentially nonsystemic treatment, which is therefore different from hormone replacement therapy, in which the hormone may be administered per os, transcutaneously, or by intravaginal administration.

On the contrary, patents EP-A-0 103 995 and US-A-5 019 395 describe galenic formulas for general hormone therapy in which the compositions have a high content of active principle, 4-15 wt% and 0.1-8 wt%, respectively, of the proprietary drug.

The proprietary drug of the invention is distinguished in particular from hormone replacement therapies administered by the vaginal route, for example in the form of creams, tablets, or vaginal suppositories, which have a high estrogen content. In this case, it is a simple matter of taking advantage of the better systemic crossover of the vaginal route as compared to the oral route, taking into account in particular that the estrogen is not metabolized when we use this route.

On the other hand, the invention is designed for local treatment, with minimum or nil systemic crossover, by direct depositing of a natural estrogen, particularly 17β-estradiol, which makes it possible to relieve local conditions and to avoid the systemic side effects that are likely to occur with certain patients, particularly endometrial hyperplasia.

Local treatments of this type have already been proposed, for example, in the form of a torus-shaped vaginal ring enclosing an estrogen that diffuses across the porous membrane of the ring, allowing for continuous release over a long period of time.

However, the disadvantage of these rings, like any intravaginal device, is that it involves the presence of a nondegradable foreign material in the body, and that it requires handling for insertion and removal.

For this local treatment, a galenic form has also been proposed containing 17β-estradiol in the form of vaginal tablets to be used daily. These tablets are matrix tables comprising an excipient such as a polymeric cellulose which absorbs traces of residual vaginal moisture to impregnate the matrix containing the active ingredient and to release it gradually.

However, because of their particular galenic form, the dose of these tablets must be relatively high to yield the desired results, typically a content of 25 μg 17β-estradiol per tablet (with one tablet corresponding to a unit dose) to allow the desired cytological, histological, and clinical improvement of the vaginal mucosa. Because of this relatively high dose, clinical studies report a proliferation of the emdometrium in some patients, which is a sign of the systemic crossover of 17β-estradiol; in particular, C. Felding et al., Preoperative Treatment with (Estradiol in Women Scheduled for Vaginal Operation for Genital Prolapse. A Randomised, Double-Blind Trail, *Maturitas*, 1992, 15, 241-249.

One of the goals of this invention is to propose a product of the above-mentioned type, with a galenic form which allows, in particular, a reduction in the dose of 17β-estradiol to avoid systemic crossover in spite of the extreme sensitivity of the

vaginal mucosa to estrogens, while obtaining a satisfactory trophic effectiveness.

According to the invention, this product is characterized by a unit galenic form including a natural estrogen chosen from 17β-estradiol and its salts in solution or in suspension in a lipophilic agent, with an estrogen content corresponding to a unit dose equivalent of 15 µg at most, preferably less than 10 µg, of 17 β-estradiol, a bioadhesive gelling hydrophilic agent, a gelling agent of the liphophilic agent, and a water-dispersible agent.

In contact with the vaginal secretions, the bioadhesive hydrophilic agent gels and, because of the presence of the water-dispersible agent, the galenic form emulsifies, which allows direct passive diffusion of the active ingredient between the emulsified excipient and the vaginal mucosa with which it is in contact. The bioadhesive nature (more specifically, mucoadhesive) of the hydrophilic gelling agent allows the emulsion to stick to the mucosa, with a low discharge, thus obtaining long-term maintenance.

This long-term maintenance makes it possible in particular to space the applications, which may be daily or less frequent (Notably in the maintenance phase).

The estrogen, advantageously micronized, may be present in galenic form, free form, or vectorized form, notably by encapsulation in vectors of the nanoparticles type such as supramolecular biovectors.

In a first implementation, the product is made in the form of a capsule comprising, on the one hand, a hard or soft solid external envelope containing gelatin, and, on the other hand, an internal liquid or semiliquid nonaqueous phase containing the

lipophilic agent with the estrogen in solution or in suspension, the bioadhesive gelled hydrophilic agent, the gelling agent of the lipophilic agent, and the water-dispersible agent.

It may be a hard capsule (capsule)* or, advantageously, a soft capsule, that is, a capsule in which the external envelope contains glycerin.

In the latter case, advantageously:

-the lipophilic agent is chosen from the liquid triglycerides;

-the hydrophilic bioadhesive gelling agent is chosen from the carboxyvinylacids, hydroxypropyl cellulose, carboxymethylcellulose, gelatin, xanthan gum, guar gum, aluminum silicate, and mixtures of these;

-the gelling agent of the lipophilic agent is hydrophobic colloidal silica;

-the water-dispersible agent is chosen from the polyoxyethylene glycols, polyoxyethylene glycol 7 glyceryl cocoate and their mixtures.

-The composition of the internal phase is: 17β-estradiol, micronized, free, or vectorized, 2.5-15 µg; hydroxypropyl cellu cellulose, 120 mg; hydrophobic colloidal silica, 50-80 mg; polyoxyethylene glycol -7 glyeryl cocate, 400 mg; liquid triglycerides, q.s. 1600 mg.

In another implementation, the product is made in the form of prolonged-release ovules, including a nonaqueous hard or soft solid homogeneous phase containing the lipophilic agent with the estrogen in solution or in suspension, the bioadhesive gelling

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* [Editor's note: Capsule occurs first in English, then French.]

hydrophilic agent, the gelling agent of the lipophilic agent, and the water-dispersible agent.

In this case, advantageously:

-the lipophilic agent is chosen from solid triglycerides with a melting point of about 35°C, carnauba wax, cocoa butter, and mixtures of these;

-the bioadhesive gelling hydrophilic agent is chosen from the carboxyvinylacids, hydroxypropyl cellulose, carboxymethylcellulose, gelatin, xanthan gum, guar gum, aluminum silicate, and mixtures of these;

-the gelling agent of the lipophilic agent is hydrophobic colloidal silica;

-the water-dispersible agent is chosen from the polyoxyethylene glycols and their mixtures;

-the composition is: 17β-estradiol, micronized, free, or vectorized, 2.5-15 μg; hydroxypropyl cellulose, 80 mg; hydrophobic colloidal silica, 5-60 mg; polyoxyethylene glycol, 50-200 mg; carboxyvlinyl acid, 8 mg; solid triglycerides, q.s. 1600 mg.

These formulations, in either case, have numerous advantages:

-they are well tolerated, stable, and galenically acceptable;

-they obtain bioadhesion, making it possible to avoid the discharge phenomenon as much as possible;

-they ensure the compatibility of the vehicles with the active ingredient;

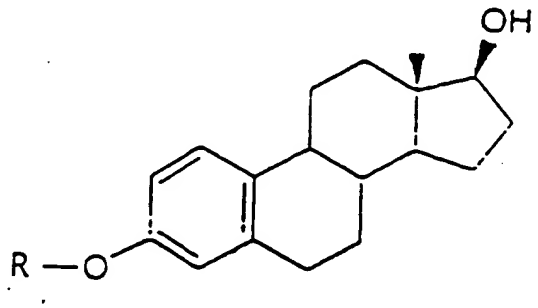
-they favor emulsification of the vehicle containing the active ingredient with the vaginal secretions, by providing a certain hydrophilic character.

We will now describe the various aspects of this invention in more detail, by giving several examples of formulations.

Choice of the active ingredient

For the product of the invention, we chose an estrogen selected from 17β-estradiol, its salts and derivatives.

This group includes the family of compounds whose chemical structure corresponds to the following general formula:



When R = H, the compound is 17β-estradiol, which is the natural hormone produced physiologically by the ovaries of fertile women, and the lack of which is responsible for the functional disorders experienced by menopausal patients.

The substance 17β-estradiol is a physiological estrogenic agonist. Its trophic role on the vulvovaginal mucosa is known, and has been described in detail, along with the reversibility of functional and clinical histological disorders by the administration of 17β-estradiol. Estradiol and its derivatives (salts) lower the vaginal pH and increase the difference in transvaginal potential, the quantity of vaginal secretions, and the local blood discharge.

In women, receptors with a high affinity for estradiol have been detected in the vaginal epithelium. For radio labeled estradiol, these receptors have an affinity similar to that calculated for the receptors of the myometrium, but they appear to be fewer in number. These receptors are characterized by a decreasing affinity for the following compounds: 17β-estradiol > estriol > estrone.

But whereas 17β-estradiol is a pure agonist, estriol, its natural metabolite, is characterized by partial agonist properties, even antagonist. There may be an antagonist effect with respect to natural estrogen.

Therefore, treatment with 17β-estradiol presents the advantage of the added effects in the presence of endogenous estradiol, whereas treatment with estriol presents the disadvantage of an antagonist effect with respect to endogenous estradiol. In addition, estriol, because its intrinsic activity is weaker than that of that of 17β-estradiol, is less active (some authors explain this phenomenon by a greater rate of dissociation of its nuclear receptors).

Since the activity presented by a partial agonist is more dependent on the number of receptors than that of the complete agonist, the difference in activity between these two estrogen compounds is more pronounced than the per unit area of vaginal tissue receptors apparently lower than at the level of the myometrium.

In conclusion, in view of the high degree of affinity of 17β-estradiol for vaginal estrogen receptors, and especially its activity profile as a complete agonist, this natural estrogen constitutes a better choice than estriol for obtaining a local trophic effect.

The same remarks are applicable to estrone, which is a precursor of estriol, as well as to the synthetic derivatives of estradiol such as, in particular, estradiol diethéroxide [methoxypropoxy estnatriene] (promestriene INN).

Choice of dose

The dose should be chosen to relieve local symptoms and to avoid transvaginal absorption as much as possible.

To achieve these goals, we select a dose of 10 µg 17β-estradiol, corresponding to a unit dose (one administration per day, or even less frequently).

When 17β-estradiol is present at this dose in free micronized form, there is only a very slight systemic crossover, in the form of a simple plasma peak about one hour after administration; the maximum plasma concentration of the peak never exceeds 30 pg/mL, but it is, of course, very transitory.

Nevertheless, if we wish to avoid even this limited crossover, a first solution consists of reducing the content of active ingredient, typically to doses of 5 µg or even 2.5 µg per individual administration.

Another possibility is to use the same excipient and vectorize the active ingredient instead of adding it in free form.

Below, we will explain the value of this vectorization and how it can be effected.

Vectorization of 17β-estradiol

One of the purposes of vectorization of 17β-estradiol is to eliminate any systemic crossover of the active ingredient by more gradual release of this ingredient, which would have the effect

of "spreading out" the plasma peak by reducing its maximum amplitude, which could always remain below 50 pg/mL of plasma concentration.

Advantageously, the vectorization will also make it possible to increase the duration of local action of the active ingredient.

These two goals can be attained as follows;

To avoid any systemic crossover, the size of the vector should be sufficiently large so that it will not pass through the vaginal epithelium. A size on the order of 200 nm in diameter meets this criterion. Of course, the vector must be compatible with 17β-estradiol, allow its gradual salting out, it should be compatible with the vaginal mucosa and perfectly well tolerated.

To increase the duration of action, it is possible to choose a system of bioadhesion by electrostatic interactions. In fact, under normal conditions, the vaginal mucus is acid (pH about 4), while at menopause this pH tends to increase to about 6. Therefore, it is advantageous to include in the periphery of the vector positive charges which can interact with the negative charges of the mucus.

We should note that the acid properties required for maximum interaction between the mucus and the vector are reduced during menopause (pH about 6), but these conditions of weak acidity may be sufficient for an effective interaction with the vectors.

A vector which fulfills these various conditions is, for example, comprised of nanoparticles (that is, particles whose diameter is on the order of a few tens or at most a few hundred nanometers) such as the "supramolecular biovectors" (SMBV) described in WO-A-89/11271 (National Center for Scientific Research) and produced by Biovector Therapeutics, Inc.

These SMBV, which are known vectors, include a nonliquid hydrophilic nucleus, an internal lipid envelope linked to the nucleus by covalent bonds, and an external amphiphilic envelope linked to the internal lipid envelope by hydrophobic interactions.

These vectors may be loaded with an active ingredient, in this case with 17β-estradiol (which is lipophilic) encapsulated in the vector, the whole then forming an active ingredient transporter which is biomimetic of the endogenous transport systems such as that of the lipoproteins.

Example of formulation of a soft capsule

To satisfy the concept of bioadhesion of the galenic form of the invention and avoid the discharge phenomenon as much as possible, the internal phase of this soft capsule contains in this example biocompatible gelling hydrophilic bioadhesive polymers which can incorporate a maximum quantity of vaginal secretions to increase viscosity and prolong the maintenance in situ of the emulsion.

Moreover, the phenomenon of discharge of the lipophilic content of the internal phase of the capsule is avoided by the use of a gelling agent of this lipophilic agent. In this example, at least one of the ingredients of the internal phase favors the emulsification with the vaginal secretions of the lipophilic derivative which is the essential constituent of the fatty phase.

A typical composition of the internal phase is as follows:

17β-estradiol, micronized, free, or vectorized	2.5 - 15 µg (or 1.5626 to 9.375 ppm)
Hydroxypropyl cellulose (Klucel® HXF)	120 mg
Hydrophobic colloidal silica (Aerosil® R972)	70 mg
Polyoxyethylene glycol glyceryl-cocoate (Cetiol® HE)	400 mg
Liquid triglycerides (Miglyol® 812)	q.s. 1600 mg

We should note the very low final concentration of active ingredient, which is 1.5625×10^{-6} to 9.375×10^{-6} for the range of unit doses indicated above, in particular 6.25×10^{-6} (0.000625%) in the case corresponding to the clinical trials which will be reported below.

This internal phase is introduced after it is prepared in an external envelope containing gelatin/glycerin and corresponding to a soft capsule structure.

A number of variations of dose of the excipients may be considered. Thus, the dose of hydrophobic silica may be between 50 and 80 mg.

It is also possible to modify the composition of the excipients.

Thus, it is possible to replace the bioadhesive gelling hydrophilic polymer (hydroxypropyl cellulose) with other bioadhesive gelling hydrophilic components, such as: carboxyvinylacids, hydroxypropyl cellulose, carboxymethylcellulose, gelatin, xanthan gum, guar gum, aluminum silicate, or a mixture of two or more of the preceding components.

As for the water-dispersible agent, of polyoxyethylene glycol -7 glycerylcocoate can be replaced by a polyoxyethylene glycol (PEG).

Example of the formulation of a prolonged-release ovule

In this case, the product includes a hard or semi-soft solid homogeneous phase whose typical composition is as follows:

17β-estradiol, micronized, free, or vectorized	2.5-15 µg
Hydroxypropyl cellulose (Klucel® HXF)	80 mg
Hydrophobic colloidal silica (Aerosil® R 972)	40 mg
Polyoxyethylene glycol (PEG 400)	80 mg
Carboxyvinylicacid (Carbopol® 974 P)	8 mg
Solid triglycerides (Witespol® S 51)	q.s. 1600 mg

The quantities of excipients used may vary. Thus, the dose of hydrophobic colloidal silica may be between 5 and 60 mg, and that of PEG between 50 and 200 mg.

It is also possible to modify the composition of the excipients.

Thus, Witespol® S 51 can be replaced by carnauba wax, cocoa butter, or other triglycerides with a melting point of about 35°C, for example Ovucire®.

These bioadhesive gelling hydrophilic polymers (Klucel® and Carbopol®) may be replaced by the same substituents as those indicated above in the example of a formulation of a soft capsule.

PEG 400 may also be replaced by a PEG 200-4000, in appropriate proportions.

Clinical trials

The results obtained on six patients indicate the following elements:

Clinical and biological tolerance: Under the conditions of the trial, the local and general clinical tolerance of the formulation above according to the invention, presented in the form of soft capsules containing doses of 2.5 µg, 5 µg, and 10 µg was excellent. No undesirable events were reported. The biological tolerance was excellent. No clinically significant anomalies were reported.

Pharmacokinetic analysis: From a pharmacokinetic standpoint, the plasma concentrations of estradiol remain unquantifiable in all the subjects after administration of the low doses (2.5 and 5 µg) and in half of the subjects at the high dose (10 µg). In the other three subjects, the levels of estradiol higher than the limit of quantification were measured after treatment only in a few samples (2 or 3) and do not exceed 30 pg/mL.

With respect to the estrone, the concentrations measured after treatment are generally of the same order of magnitude as those measured before treatment. in fact, when the levels of estrone are higher after treatment (2 or 3 subjects per group, depending on the group), the highest concentration does not exceed by more than 22% (subject No. 2), 34% (subject No. 6), and 26% (subject No. 6) the values measured before treatment, at 2.5 µg, 5 µg, and 10 µg 17β-estradiol, respectively. In all cases, the concentrations of estrone never exceed 30 pg/mL. The examination of the profiles of plasma concentrations of estrone show that there is not proportionality between the C_{max} or the SSC [expansion unknown] and the dose administered.

General conclusion: After a single vaginal administration of a soft capsule containing 2.5 µg, 5 µg, and 10 µg 17β-estradiol, the clinical tolerance was excellent for all six subjects included in the test. The biological tolerance was also excellent. No clinically significant anomalies were reported.

Form the pharmacological standpoint, the vaginal resorption of the estradiol was nil after administration of capsules containing 2.5 and 5 µg 17β-estradiol. After administration of the capsule containing 10 µg of 17 β-estradiol, the estradiol remained undetected in the plasma in three out of six subjects. For the other subjects, some plasma concentrations of estrone show that the levels measured after treatment are comparable to the levels measured before treatment. Therefore, we can conclude from this study that the vaginal absorption of estradiol from the soft capsules containing 2.5 µg and 10 µg 17β-estradiol is almost nil in the range of doses tested.

In particular, we should note the absence of a peak higher than 50 pg/mL, the limit beyond which side effects may appear in certain subjects (supra). The free form, micronized, of 17β-estradiol is completely satisfactory, and does not require recourse to a vectorized form to avoid exceeding the threshold of 50 pg/mL. However, this vectorized form might be considered if we wish to prolong the time of action of the active ingredient.

Claims

1. A proprietary drug for local, essentially nonsystemic treatment of vaginal dryness, particularly in the menopausal woman, characterized by a unit galenic form comprising a natural estrogen chosen from 17β-estradiol and its salts in solution or

in suspension in a lipophilic agent, with an estrogen content corresponding to a unit dose equivalent to a maximum of 15 μg, preferably less than 10 μg, of 17β-estradiol, a bioadhesive gelling hydrophilic agent, a gelling agent of the lipophilic agent, and a water-dispersible agent.

2. The product of Claim 1, in which the estrogen is present in free form, advantageously micronized.

3. The product of Claim 1, in which the estrogen is present in vectorized form, advantageously micronized.

4. The product of Claim 3, in which the estrogen is vectorized by encapsulation in nanoparticle vectors.

5. The product of Claim 4, in which the estrogen is vectorized by encapsulation in particular vectors of the supramolecular biovector type.

6. The product of Claim 1, in capsule form comprising, on the one hand, a hard or soft external solid envelope containing gelatin and, on the other hand, an internal liquid or semiliquid nonaqueous phase containing the lipophilic agent with the estrogen in solution or in suspension, the bioadhesive gelling hydrophilic agent, the gelling agent of the lipophilic agent, and the water-dispersible agent.

7. The product of Claim 6, in the form of a soft capsule, in which the external envelope contains glycerin.

8. The product of Claim 6, in which the lipophilic agent is chosen from the liquid triglycerides.

9. The product of Claim 6, in which the bioadhesive gelling hydrophilic agent is chosen from the carboxyvinylacids, hydroxypropyl cellulose, carboxymethylcellulose, gelatin, xanthan gum, guar gum, aluminum silicate and mixtures of these.

10. The product of Claim 6, in which the gelling agent of the lipophilic agent is hydrophobic colloidal silica.

11. The product of Claim 6, in which the water-dispersible agent is chosen from the polyoxyethylene glycols, polyoxyethylene glycol -7 glyceryl cecoate and their mixtures.

12. The product of Claim 6, in which the composition of the internal phase is:

17β-estradiol micronized, free, or vectorized	2.5-15 µg
Hydroxypropylcellullose	120 mg
Hydrophobic colloidal silica	50-80 mg
Polyoxyethylene glycol glyceryl cocoate	400 mg
Liquid triglycerides	q.s. 1600 mg

13. The product of Claim 1, in the form of a prolonged-release ovule comprising a hard or semisoft nonaqueous solid homogeneous phase containing the lipophilic agent with the estrogen in solution or in suspension, the bioadhesive gelling hydrophilic agent, the gelling agent of the lipophilic agent and the water-dispersible agent.

14. The product of Claim 13, in which the lipophilic agent is chosen from the solid triglycerides with a melting point of about 35°C, carnauba wax, cocoa butter, and their mixtures.

15. The product of Claim 13, in which the bioadhesive gelling hydrophilic agent is chosen from the carboxyvinylacids, hydroxypropyl cellulose, carboxymethylcellulose, gelatin, xanthan gum, guar gum, aluminum silicate, and their mixtures.

16. The product of Claim 3, in which the gelling agent of the lipophilic agent is the hydrophobic colloidal silica.

17. The product of Claim 13, in which the water-dispersible agent is chosen from the polyoxyethylene glycols and their mixtures.

18. The product of Claim 13, whose composition is:

17β-estradiol micronized, free, or vectorized	2,5-15 ug
Hydroxypropyl cellulose	80 mg
Hydrophobic colloidal silica	5-60 mg
Polyoxyethylene glycol	50-200 mg
Carboxyvinylacid	8 mg
Solid triglycerides	q.s. 1600 mg

INTERNATIONAL SEARCH REPORT

Int. ...nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 103 995 (CILAG AG) 28 March 1984 see claims 1-3 see page 2, line 5 - page 3, line 35	1,2,6, 8-11, 13-17
Y	US,A,5 019 395 (MAJID MAHJOUR, ET AL.) 28 May 1991 see claims 1,3 see column 3, line 25 - line 28	1,2,6, 8-11, 13-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter... nal Application No
PCT/FR 96/01555

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-103995	28-03-84	AU-B-	557476	24-12-86
		AU-A-	1833483	01-03-84
		CA-A-	1207231	08-07-86
		GB-A,B	2126086	21-03-84
		HK-A-	99986	24-12-86
		JP-C-	1888890	21-10-94
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		US-A-	4698359	06-10-87
US-A-5019395	28-05-91	AU-A-	3025889	14-09-89
		DE-T-	68907081	21-10-93
		EP-A-	0332147	13-09-89
		EP-A-	0499662	26-08-92
		ES-T-	2056981	16-10-94
		IE-B-	62871	08-03-95
		JP-A-	1272519	31-10-89